EFFECT OF LURASIDONE ON COGNITION: FROM LAB TO CLINIC

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INTRODUCTION

- Cognitive dysfunction is a common and clinically relevant impairment in schizophrenia that is correlated with functional outcomes in real-world settings.[1,2] For this reason, improvement in cognitive function has long been recognized as a major goal in the treatment of schizophrenia[3,4]
- Lurasidone is an atypical antipsychotic that has been approved by the FDA for the treatment of schizophrenia and bipolar depression; and has been approved for the treatment of schizophrenia by SwissMedic and Health Canada

OBJECTIVE

- To summarize published literature on the pre-clinical behavioral evidence that lurasidone may have an effect on cognitive function (including relevant receptor binding and other potential CNS mechanisms); and to review the results of the first randomized, double-blind, placebo-controlled trial (6 weeks; with a 6-month extension phase) that evaluated the efficacy of lurasidonefor treating cognitive deficits in patients with an acute exacerbation of schizophrenia

RECEPTOR BINDING AND POTENTIAL CNS MECHANISMS

Table 1. Lurasidone: Receptor Binding Profile

Receptor	Binding Affinities (Ki, nM) [5]	Potential Clinical Implications
Serotonin 5-HT$_7$	0.495	Potent antagonist: pre-clinical evidence that 5-HT$_7$ is involved in hippocampus-dependent contextual learning and memory processing; and potential antidepressant effects [8-10]
Dopamine D$_2$	1.68	Potent antagonist: antipsychotic effects
Serotonin 5-HT$_{2A}$	2.03	Potent antagonist: may reduce EPS and need for anticholinergic medications
Serotonin 5-HT$_{1A}$	6.75	High affinity partial agonist: potential anxiolytic and antidepressant effects [6,7]
Histamine H$_1$	>1000[a]	Negligible activity: lurasidone unlikely to be associated with sedative or anticholinergic effects that might have an adverse effect on cognition and memory
Acetylcholine M$_1$	>1000[a]	

[a] IC_{50} value n.t.: not tested; EPS: extrapyramidal symptoms

- Lurasidone has moderate affinity for norepinephrine α_1, α_{2A}, and α_{2C} receptors; weak affinity for D_1 and 5-HT_{2C} receptors; and negligible affinity for multiple other receptors including histamine H_1, muscarinic, nicotinic, glutamate and sigma receptors, as well as dopamine and serotonin transporters

Lurasidone and Cognitive Function: Potential Mechanisms

Glutamate and NMDA

- Glutamate has been hypothesized to play a role in schizophrenia. Reduced activity at the N-Methyl-D-aspartate (NMDA) receptor has been implicated as a potential mechanism in the cognitive deficits observed in patients with schizophrenia[16]
- Treatment with lurasidone has been shown to produce enhancement of NMDA-receptor-mediated synaptic responses, an effect that may be related to the 5-HT_7 receptor antagonism[17]
- In the phencyclidine (PCP) model of psychosis, lurasidone has been shown to restore NMDA-receptor-mediated synaptic responses to normal suggesting that the procognitive effects of lurasidone may be mediated, in part, by glutamatergic mechanisms[18]

BDNF and Neuroplasticity

- Schizophrenia is characterized by reduced neuroplasticity. One key biomarker of neuronal plasticity is the neurotrophin brain-derived nerve factor (BDNF). Expression of BDNF has been reported to be reduced in patients with schizophrenia[19,20]
- In several studies, chronic treatment with lurasidone has been shown to up-regulate BDNF expression, both in rat prefrontal cortex[21] and in the ventral hippocampus[22]
- Chronic treatment with lurasidone has also been shown to increase hippocampal BDNF transcription following an acute stress[21]

Metabolomic Correlates of Antipsychotic Response

- In a short-term, double-blind, placebo-controlled trial, an increase in serum glutamate was associated with improvement in negative symptoms among patients with an acute exacerbation of schizophrenia who responded to lurasidone treatment
- A significantly greater increase in glutamate levels were observed in the subgroup of responders who achieved the greatest improvement in negative symptoms[23]

COGNITIVE EFFECTS OF LURASIDONE IN PRECLINICAL MODELS

Table 2. Summary of Preclinical Studies of Lurasidone: Battery of Cognition and Memory Tests

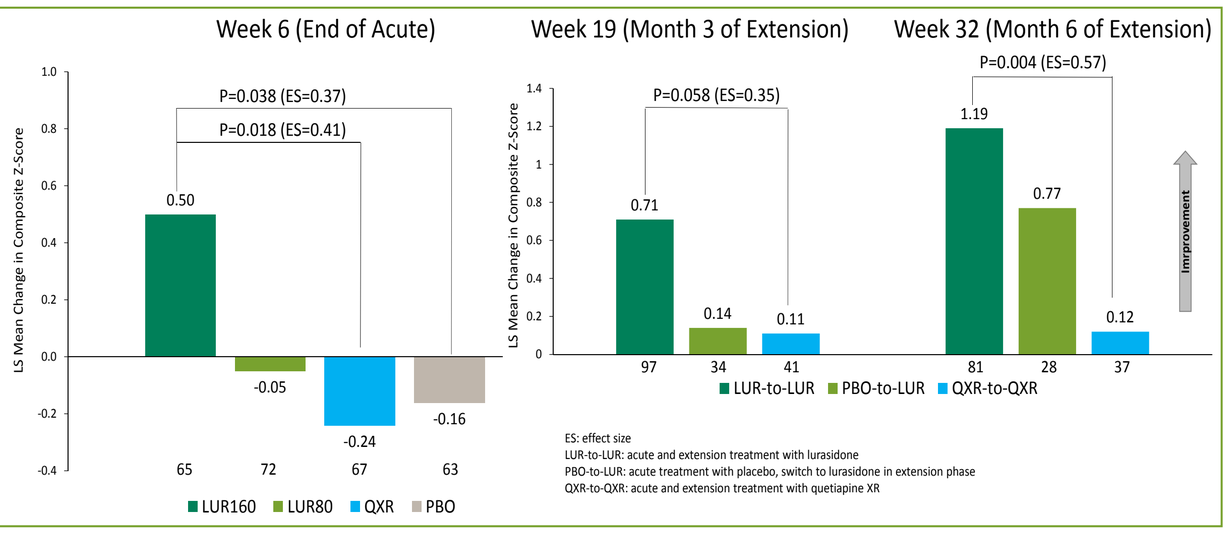
Preclinical model	Results	Cognitive Effect of Lurasidone in Pre-clinical Model
Passive avoidance test (rodent model) (with MK-801-induced impairment)[11]	• Lurasidone significantly reversed MK-801-induced impairment in the passive avoidance response	• Improvement in learning and memory
Radial arm test (rodent model) (with MK-801-induced impairment)[12]	• Lurasidone significantly reduced the number of reference memory errors, and showed a trend reduction in the number of working memory errors	• Improvement in spatial learning and memory function (working and reference memory)
Morris water maze test (with MK-801-induced impairment)[12]	• Lurasidone significantly decreased escape latency, swimming distance, and frequency of diving behaviors	• Improvement in spatial learning, memory, and cognitive mapping
Novel Object Recognition test (NOR; rodent model) (with PCP-induced impairment. The NOR test has been hypothesized to be an analog of declarative memory)[13,14]	• Lurasidone significantly improved the sub-chronic PCP-induced NOR deficit. The ability of lurasidone to improve PCP-induced NOR deficits appears to be mediated (at least in part) by 5HT_7 antagonism, since the effects were blocked by use of a 5-HT_7 receptor agonist	• Improvement in short-term and intermediate-term object recognition memory; this effect was shown to be mediated by antagonist activity at the 5-HT_7 receptor
Object Retrieval with Detour task (ORD; marmosets)[15]	• Lurasidone dose-dependently increased retrieval success rate in a difficult ORD task	• Improvement in task performance related to attention, behavioral inhibition, and executive function

- MK-801 and phencyclidine (PCP) are both non-competitive NMDA antagonists used in animals as a pharmacologic model of schizophrenia
- In this battery of pre-clinical tests, lurasidone restored MK-801-induced learning and memory impairment in the passive avoidance, Morris water maze test, and the radial arm maze test
- Treatment with lurasidone also improved sub-chronic PCP- induced deficits in novel object recognition and memory in rats, and increased the success rate of marmosets in performing a difficult object retrieval task

COGNITIVE EFFECTS OF LURASIDONE IN A CLINICAL TRIAL

- The potential effectiveness of lurasidone in treating cognitive deficits associated with schizophrenia has been evaluated in a trial where patients with an acute exacerbation of schizophrenia were randomized to 6 weeks of double-blind, placebo-controlled treatment with lurasidone or quetiapine-XR[24]
- Upon completion of the initial 6-week study, eligible patients were enrolled in a 1-year, double-blind extension study, where patients continued treatment with either flexible-dose lurasidone 40–160 mg/d or quetiapine-XR 200–600 mg/d[25]
- The CogState computerized cognitive battery was a secondary outcome measure that was administered at pre-treatment baseline, week 6 (end of acute phase study), and weeks 19 and 32 (months 3 and 6 of the extension phase) by trained raters

Figure 1. Treatment with Lurasidone on Neurocognitive Composite Score: LS Mean Change in Z-Scores (Evaluable Sample Analysis)



- The composite z-score is an average of the standardized z-scores for each of the 7 cognitive domains tested on the CogState computerized cognitive battery
- For the evaluable sample with valid CogState scores at week 6, lurasidone 160 mg was found to be significantly superior to both placebo and quetiapine XR on the neurocognitive composite score at month 6, while lurasidone 80 mg, quetiapine XR, and placebo did not differ
- During the extension phase, lurasidone (flexibly dosed) continued to demonstrate higher neurocognitive composite scores compared with quetiapine XR

Figure 2. Heatmap of Change From Baseline to Week 19 or Week 32 in the Neurocognitive Composite and Individual Domain Z-scores

	Week 19 Change Scores (month 3 of extension)				Week 32 Change Scores (month 6 of extension)			
	LUR160 → LUR	LUR80 → LUR	PBO → LUR	QXR600 → QXR	LUR160 → LUR	LUR80 → LUR	PBO → LUR	QXR600 → QXR
Neurocognitive Composite	***		**		***	**	*	
ISLT Verbal Learning	**		**		***	*	*	
OCL Visual Learning	**	**				**	*	
ONB Working Memory	*	*				***	*	
GMLT Reasoning	**	***			***	***	*	*
DET Speed					‡	**		
IDN Attention						*		
SECT Social Cognition	**	*	*	*	**	**		

NS ‡P<0.10 *P<0.05 **P<0.01 ***P<0.001

Data shown for full analysis sample

- The heatmap shows the pattern of significant findings on individual cognitive domains at weeks 19 and 32 during the extension study. Treatment with lurasidone was associated with sustained benefit across multiple cognitive domains when compared with quetiapine XR

CONCLUSIONS

- These findings provide preliminary clinical evidence that is consistent with pre-clinical data demonstrating the potential of lurasidone for improving cognitive function in patients with schizophrenia
- Clinical assessment of the longer term effects of lurasidone on cognition requires additional investigation
- Development of improved preclinical models of cognitive impairment will help to identify and develop agents with clinically useful drug effects in humans

DISCLOSURES

Dr. Harvey is a consultant for Abbott Labs, Boeheringer-Ingelheim, EnVivo, Genentech, Otsuka-America, Roche Pharma, Sunovion Pharma, and Takeda Pharma. Drs. Pikalov, Cucchiaro and Loebel are employees of Sunovion Pharmaceuticals Inc. Dr. Siu is a paid consultant to Sunovion Pharmaceuticals Inc and Takeda Pharmaceuticals Inc.

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